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EXAMINER	
ALONZO, NORMA LYN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/679,231	HOLLAND, ERIC CHARLES	
	Examiner	Art Unit	
	Norma C Alonzo	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) 5-17 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-4 and 18-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 03 October 2003 and 08 March 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 7/12/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 1-20 are pending in the instant application

2. Applicant's election without traverse of Group 1, claims 1-4 and 18-20, drawn to a non-human transgenic animal expression a reporter gene coding for a protein capable of producing light upon metabolizing a substrate wherein said reporter gene is operably linked to a promoter which is activated by cell cycling, in the reply filed on 10/3/04 is acknowledged.

3. Claims 5-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/3/04.

4. Claims 1-4 and 18-20 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-4 and 18-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse expressing a reporter gene coding for a firefly luciferase protein, wherein said reporter gene is operably linked to an E2F1 promoter, does not reasonably provide enablement for any non-human transgenic animal expressing a reporter gene coding for any protein that is capable of producing light upon metabolizing a substrate, wherein said reporter gene is operably linked to any promoter which is activated by cell cycling. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400 , 1404 (Fed. Cir. 1988)). Furthermore, USPTO does

not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompasses any non-human transgenic animal expressing a reporter gene encoding any protein capable of producing light upon metabolizing a substrate, which is operably linked to any promoter, wherein said promoter is activated by cell cycling.

The invention is in the nature of transgenic animals. The art of transgenic animals has for many years stated that unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have, within their cells, cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the geneome (Kappel, et al. (1992) Current Opinion in Biotechnology, 3: 549, col. 2, paragraph 2). Mullins et al. (1993) states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes (Mullins, et al. (1993) Hypertension 22, page 631, col. 1, paragraph 1, lines 14-17). The elements of the particular construct used to make the transgenic animal are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene, e.g., specific promoters, presence or absence of introns, etc. (Houdebine (1994) J. Biotech., 34, page

281). "The position effect" and unidentified control elements also are recognized to cause abberant expression (Wall (1996) Theriogenology 45, page 61, paragraph 2, line 9 to page 62, line 3). Mullins et al. (1996) discloses that "the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another." (Mullins, et al. (1996) J. Clin. Invest., 98, page S39, Summary). Well regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron (1997) Molec. Biol., 7, page 256, paragraph bridging cols. 1-2). Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron (1997) Molec. Biol., 7, page 256, lines 10-13). Further, Sigmund states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus, the phenotype observed (Sigmund (2000) Arteroscler. Throm. Vasc. Biol. 20, page 1426, col. 1, paragraph 1, lines 1-7). With regard to the import of promoter selection, Niemann states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to, the other compatible with, pig health (Niemann (1997) Transg. Res. 7, page 73, col. 2,

In regards to the claimed embodiment comprising any promoter that is activated by cell cycling, the art of cell-cycle-sensitive promoters teaches that there are several

genes whose promoters are activity-dependent on the cell cycle. For example, there are positive and negative growth-regulatory signals acting during the G1 state of the cell cycle including the cyclins, the cyclin-dependent kinases (Cdks), the inhibitors of Cdk's, and the tumor suppressor genes (Rb, p53, and p19). Additionally, Sandal T teaches "the components of the different cell cycle phases crosstalk with each other and other components." Wherein the claimed invention comprises any promoter that is activated by cell cycling, enablement for the full embodiment of the invention comprises these positive and negative growth-regulatory signals as well as other components that may crosstalk with these signals. The state of the art of cell cycle-sensitive promoters teach that even the major players of cell cycling comprise factors that are diverse and heterogenous such as c-Myc for Cyclin D and E2F for Cyclin E.

In regards to the claimed embodiment comprising any protein capable of producing light upon metabolizing a substrate, the art teaches "'luciferase' is a family of photo-proteins that can be isolated from a large variety of insects, marine organisms, and prokaryotes. Luciferase proteins catalyzing the light-emitting reactions of firefly, coelenterates, or bacteria show no nucleotide homology to each other. The substrates "luciferin of these reactions are also chemically unrelated." Specific guidance to use a particular luciferase, therefore, does not necessarily predict guidance to use another luciferase. For example, Bhaumik and Gambhir (PNAS 99(1): 377-382, 2002) teach imaging of Rluc (Renilla luciferase) and Fluc (firefly luciferase) and show that the kinetics of light production are distinct wherein "light from Rluc-carrying cells quickly peaks and rapidly extinguishes whereas light from Fluc-carrying cells peaks later and

persists longer." (page 382, paragraph 2) Further, the full embodiment of the claimed invention also encompasses reporter genes coding for non-luciferase proteins. Again, specific guidance to use a reporter gene that encodes firefly luciferase does not necessarily predict guidance to use a reporter gene that encodes any protein capable of producing light upon metabolizing a substrate because there are no known common structures or coding sequences that distinguish said proteins. Further, Vooijs et al., in discussing luciferase signal in bioluminescence imaging of spontaneous tumor formation, teach "in addition to signal location, signal strength is another parameter that determines sensitivity, which is determined by many factors including the number of luciferase-expressing cells, the promoter used to drive luciferase expression, the transgene copy number, and the transgene integration site." (page 1866, paragraph 2) Therefore, the art of mouse transgenesis is unpredictable in view of the large genus of promoters encompassed by the claimed invention and the unpredictability of the art of promoters in animal transgenesis and the large genus of reporter genes encompassed by the claimed invention and the unpredictability of the art of bioluminescence. While the level of skill of an artisan practicing the claimed invention will be high, in view of the unpredictability of the state of the art, an artisan would require specific guidance from the instant specification to carry out the full breadth of the claimed invention.

The specification broadly teaches a non-human transgenic animal expressing a fusion construct that comprises one or more copies of a cell-cycle-sensitive promoter, wherein said promoter is operably linked to a reporter gene coding for a protein able to produce light upon metabolizing a substrate. However, the instant specification

provides specific guidance for making only an Elux mouse, having cells comprising the firefly luciferase transgene operably linked to an E2F1 promoter, that then is crossbred with an Ntv-a transgenic mouse. Progeny of the cross are intracranially administered a chicken fibroblast cell line infected with a RCAS-PDGF-producing virus which results in brain tumors. Whereas the instant specification provides specific guidance to generate a transgenic mouse having an E2F1 promoter operably linked to a reporter gene encoding firefly luciferase, the specific guidance provided by the instant specification to generate this Elux mouse does not enable a skilled artisan to make and use any non-human animal having cells comprising any reporter gene encoding a protein that produces light when it metabolizes its substrate, operably linked to any promoter that is cell-cycle sensitive, such that progeny of a crossbreed of said animal with the Ntv-a transgenic mouse produce offspring that have bioluminescent-detectable tumors which could be measured non-invasively, as taught in the instant specification. The instant specification does not teach any cell-cycle-sensitive promoter other than E2F1. The instant specification does not teach any other non-human transgenic animal having cells comprising firefly luciferase operably linked to any cell-cycle-sensitive promoter other than E2F1. Because the art of promoters activated by cell cycling teaches a large number of species within the genus of cell cycle-sensitive promoters and the art of reporter genes encoding proteins capable of producing light teaches a diverse and heterogenous species within the genus of bioluminescence teaches and, further, because the art of bioluminescence teaches that many factors, including the use of specific promoters, determines the predictability of the use of a transgenic animal in

bioluminescence studies, a skilled artisan would require specific guidance from the instant specification and in the absence of such specific guidance, undergo extensive experimental analysis to make and use a non-human transgenic animal having cells comprising a luciferase protein operably linked to any cell cycle-specific promoter. Because the instant specification does not provide sufficient guidance as such, it would take an undue burden of experimentation for a skilled artisan to make and use the full breadth of the claimed invention, any non-human transgenic animal having cells comprising any reporter gene encoding a protein that is capable of producing light upon metabolizing a substrate, wherein said gene is operably linked to any cell cycle-specific promoter.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the claimed invention is not enabled for its full breadth and limiting the scope of the claimed invention to a non-human transgenic mouse expressing a reporter gene encoding a firefly luciferase protein, wherein said reporter gene is operably linked to an E2F1 promoter is proper.

5. Claims 1-3 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of Claim(s) 1-3 and 18-19 encompasses a non-human transgenic animal expressing a reporter gene coding for a luciferase protein, wherein said protein is operably linked to any promoter which is activated by cell cycling.

The promoters of these claim(s) are broad in scope, being defined on the basis of their effect, and not on any specific structure. The specification broadly discloses genes that control cellular growth and differentiation, specifically oncogenes and tumor suppressor genes, wherein "the concerted activity of these two classes of genes underlie tumor development and progression." The specification further broadly teaches the cellular transcription factor, E2F, as a key player "in the malignant progression of most human malignant gliomas." (pages 14 – 17) The specification further teaches the Elux transgenic mouse line, generated using the fusion protein construct containing the E2F1 promoter with the firefly luciferase reporter protein.

In analyzing whether the written description requirement is met for gene claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification teaches the complete structure of the E2F1 promoter as including "208 nucleotides upstream, and 66 bases downstream of the transcription site. The sequence contains several binding sites for E2F1 as well as binding sites for the transcription factor SP1. This was digested with EcoR1 and Stu1 and ligated" to the firefly luciferase gene. Therefore, whereas the complete structure of the E2F1 gene construct was described, description of one promoter is an insufficient number of representative species to represent the entire genus of the claims. The specification, therefore, does not provide any disclosure as to

what would have been the required structure which would allow one to distinguish the various species of the genera. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other characteristics of the promoter is "activated by cell cycling." Such functional characteristics, however, do not allow one of skill in the art to distinguish the different members of the genera from each other because "activated by cell cycling" is a broad term and is applicable to a genus comprising a large number of species including oncogenes, tumor suppressor genes, cyclins, viruses, and cyclin-dependent kinases.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a non-human transgenic mouse having a cells expressing a luciferase protein operably linked to any promoter activated

by cell cycling, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

6. Claims 1-2 and 4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of Claim(s) 1-2 and 4 encompasses a non-human transgenic animal having cells comprising a reporter gene encoding any protein capable of producing light that is operably linked to a cell-cycle-sensitive promoter.

The proteins of these claim(s) are broad in scope, being defined on the basis of their effect, and not on any specific structure. The specification broadly discloses "modified versions of the luciferase enzyme, luciferase enzyme from different species or any other protein that can produce, pese, light able to cross animal tissues or any enzyme that can emit light able to cross animal tissues when provided with a suitable substrate." (page 17, lines 16-20) Wherein the working example in the instant specification teaches the firefly luciferase gene, the full embodiment of the invention comprises any protein capable of producing light.

In analyzing whether the written description requirement is met for gene claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification does not teach the

complete structure of the light-producing protein and the working example only teaches a fusion protein construct comprising firefly luciferase operably linked to a E2F1 promoter. Further, the instant specification does not describe any common structure or coding sequence that is shared among proteins capable of producing light or unique structures or coding sequences that would enable a skilled artisan to distinguish a light-producing protein from another light-producing protein. The specification, therefore, does not provide any disclosure as to what would have been the required structure which would allow one to distinguish the various species of the genera. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other characteristics the specification teaches about the protein is the ability to generate light when its substrate has been metabolized. Such functional characteristics, however, do not allow one of skill in the art to distinguish the different members of the genera from each other because Ghaumik and Gambhir (PNAS 99(1):377-382, 2002) teach that "luciferase is a family of photo-proteins that can be isolated from a large variety of insects, marine organisms, and prokaryotes," that they "show no nucleotide homology to each other" and that the substrates "luciferin" of these reactions are also chemically unrelated" (page 377, paragraph 4). Further, because the genus of "luciferase" comprises such a large number of species, a sufficient number of representative species of the genus would have to be described to provide an adequate written description of the claimed

embodiment to a skilled artisan. Wherein the instant specification provides an adequate written description of the only one species, firefly luciferase, the claimed genus is not sufficiently described.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of **a** non-human transgenic animal having cells expressing any luciferase protein operably linked to a cell-cycle-sensitive promoter, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-3 and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hasan et al. (Genesis 29:116-122, 2001) in view of Muller et al (Mol Cell Biol 20(9): 3316-3329, 2000).

The claims are drawn to a non-human transgenic mouse having cells expressing a reporter protein, wherein said protein is luciferase, wherein said protein is operably linked to a promoter which is activated by cell cycling.

Hasan et al. teach a non-human transgenic mouse, the POMCcre-POMCluc mouse, which serves as "a mouse model of spontaneous Rb-dependent cancer that enables noninvasive bioluminescence imaging of pituitary tumor development." (page 1862, see Materials and Methods) The POMCcre-POMCluc mouse was produced using a vector comprising the luciferase open reading frame which was cloned into a vector containing 78 nucleotides of the 5'-flanking sequence of rat POMC followed by SV40 splice and polyadenylation signals. Two founders from this line were crossed with mice carrying a conditional mutant Rb allele to obtain PMCcre-POMCluc;$Rb^{f19/+}$ mice which showed hyperplastic nodules within the pituitary intermediate lobes. (page 1863, paragraph 4) POMCcre-POMCluc;$Rb^{f19/19}$ animals developed pituitary tumors and the authors show "a good correlation between detected photons and tumor weight" and an

almost doubling of the signal over 2 weeks, indicating exponential tumor growth." (page 1864, paragraph 2) Further, the authors teach administration of doxorubicin, an S-phase-specific drug that is used to treat a diverse range of human tumor types, to POMCcre-POMCluc;$Rb^{f19/19}$ and showed steady state bioluminescence levels and tumor development, indicating the absence of neoplastic growth versus POMCcre-POMCluc;$Rb^{f19/19}$ mice not treated with doxorubicin. The authors do not teach generation of a mouse model of spontaneous cancer that enables noninvasive bioluminescence imaging of pituitary tumor development using the E2F1 gene.

Muller et al. teach that in leukemia cell lines transgenic for a cyclin A1 promoter-enhanced green fluorescent protein (EGFP), activity of the cyclin A1 promoter is dependent on methylation of its CpG site such that hypomethylation of the promoter is important for transcriptional activity of the promoter in cancer cells lines, but in HeLa cells. (page 3326, paragraph 3) The authors also teach mice that were transgenic for a cyclin A1 promoter-enhanced green fluorescent protein (EGFP) and showed that "transcriptional repression of cyclin A1 promoter activity could be established in almost all organs without CpG methylation of the transgenic promoter." (page 3327, paragraph 2) (page 3317, paragraph 3).

At the time of the invention, it would have been obvious to modify the method of Hasan et al. to make a non-human transgenic animal that expresses firefly luciferase by using the cell-cycle-sensitive promoter taught by Muller et al. A skilled artisan would have had a reasonable expectation of success because both Hasan et al. and Muller et al. were able to produce viable, tumor-forming animals. A skilled artisan would have

been motivated to modify the non-human transgenic mouse of Hasan et al. to express firefly luciferase under the control of a cell cycle-sensitive promoter as taught by Muller et al. because Hasan et al. teach that translating the knowledge of critical pathways involved in tumorigenesis is a major challenge and while tumor-prone mice with genetically defined alterations are potentially of great value for gaining insight into the etiology and treatment of cancer, the stochastic nature of tumor onset in mouse models of sporadic cancer complicates efficient testing of anticancer drugs because large number of animals are required to obtain statistically reliable results. Therefore, noninvasive methods that permit longitudinal monitoring of tumor growth and drug response, such as bioluminescence, would greatly reduce the number of mice required for these studies and broaden the scope of analyses that can be performed." Further, Muller et al. teach that "abnormalities in CpG methylation are involved in tumorigenesis and senescence" (page 3316, paragraph 3) and that "methylation of CpG dinucleotides," such as those found within the cyclin A1 promoter region, "is thought to be involved in imprinting and in the pathogenesis of cancer." (page 3316, paragraph 1) Therefore, utilizing the bioluminescence model of Hasan et al. to further delineate the involvement of a cell cycle-sensitive promoter in cancer as taught by Muller et al. would be obvious.

Conclusion

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Norma C Alonzo whose telephone number is 571-272-2910. The examiner can normally be reached on 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NCA

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER